PAPERS AND ORIGINALS

Intravenous infusion of salbutamol in severe acute asthma

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Summary and conclusions

Out of 62 asthmatic patients admitted to hospital with an acute exacerbation of their disease, those whose symptoms had not sufficiently improved 15 minutes after an initial intensive regimen were randomly allocated to receive an intravenous infusion of either salbutamol 10 μg/min (20 patients) or aminophylline 1 mg/min (19 patients). During the infusions, which lasted 36 hours, peak expiratory flow rates and spirometric values improved in both groups, but differences between the groups did not achieve statistical significance.

Although salbutamol may be infused safely for a prolonged period to patients with acute asthma, it has no particular advantage over aminophylline. Furthermore, in patients who respond poorly to initial intensive treatment the subsequent infusion of a bronchodilator may not increase the rate of recovery from the rate that would occur naturally.

Introduction

Salbutamol given by mouth or inhalation is an effective bronchodilator in the routine management of asthma[1] but may become ineffective during an acute attack, when parenteral administration of a bronchodilator may be required.[2] Intravenous aminophylline is often used[3] but may have unpleasant side effects.[4] Salbutamol, a beta$_2$-selective adrenoceptor agonist, may be clinically important if intravenous administration achieves as efficient a bronchodilatory effect as that of aminophylline in acute asthma. Only one study comparing intravenous administration of these drugs to patients with acute asthma has been carried out, in which the infusions lasted one hour.[5] Many attacks of asthma, however, require treatment for considerably longer than this. We report the effects of infusing salbutamol and aminophylline over 36 hours in asthmatic patients whose acute attacks had failed to respond to an initial intensive regimen.

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Patients and methods

Consecutive patients aged 16-65 years admitted to the high-dependence medical ward of this hospital with acute asthma were included in the trial provided they had no history of cardiovascular or renal disease. All patients received an initial regimen of aminophylline 5 mg/kg body weight injected intravenously over 10 minutes while they breathed supplementary oxygen, followed 15 minutes later by two inhalations of nebulised salbutamol (5 mg each) given by intermittent positive-pressure breathing (IPPB). Intravenous hydrocortisone 200 mg was also given and oral prednisone 40 mg daily begun. If the patient was already taking corticosteroids prednisone was increased to 40 mg daily in divided doses.

Fifteen minutes after completing this regimen—that is, about 75 minutes after admission—the patients were assessed by the physician responsible for their care. If they were considered not to need further intravenous treatment they were removed from the study; otherwise they were allocated at random to intravenous infusion of either salbutamol 10 μg/min or aminophylline 1 mg/min. During the infusion period all the patients received a standard supportive regimen comprising nebulised salbutamol (5 mg) given four times a day by IPPB, corticosteroids, supplementary oxygen, and physiotherapy. Antibiotics were prescribed as necessary. The physician responsible for each patient knew which infusion drug had been allocated. If at any time he considered the progress of the patient to be unsatisfactory he could substitute the other infusion. Similarly he could discontinue the infusion when he judged the asthma to be adequately controlled.

In each case we measured heart rate and blood pressure; peak expiratory flow rate (PEFR) with a Wright peak-flow meter; and forced expired volume in one second (FEV_1) and forced vital capacity (FVC) by a dry bellows spirometer (Vitalograph). Measurements were taken on admission, 15 minutes after completing the initial regimen, and at regular intervals during the infusion period (at least

three and a half hours after any administration of nebulised salbutamol and if possible just before the next inhalation). An arterial blood sample for assessing pH and blood gas tensions was taken routinely from each patient on admission, before the oxygen and drug treatment.

Statistical analyses were carried out with Student's paired and unpaired *t* tests.

Results

Sixty-two patients entered the study. After the initial regimen 23 were considered to have improved sufficiently not to require infusion of a bronchodilator (no infusion group). The remaining 39 patients were allocated to receive either a salbutamol infusion (20 patients) or an aminophylline infusion (19 patients).

On admission 30 of the 62 patients were regularly taking oral corticosteroids, 54 were receiving salbutamol by tablet or aerosol, and 26 were taking methylxanthine derivatives. The distribution of patients receiving corticosteroids or salbutamol or both was similar between the groups, but 14 (74%) of the patients in the aminophylline group were receiving methylxanthine derivatives as compared with only 6 (30%) in the salbutamol group and 6 (26%) in the no infusion group. The three groups were closely matched for age, height, and weight, but there were fewer men in the aminophylline group (table I).

In all groups the mean PEFR, FEV_1, FVC, and arterial blood gas tensions on admission were similar, and 15 minutes after the initial regimen was completed the mean PEFR, FEV_1, and FVC had increased significantly (table II). There was a significantly greater increased in PEFR and FEV_1 in the no infusion group than in the other two groups ($P<0.001$). Heart rate fell in the no infusion group but rose in the others. All groups showed a fall in systolic blood pressure, which was significant in only the no infusion group ($P<0.01$).

At the start of the infusions the salbutamol and aminophylline groups had similar mean values of PEFR, FEV_1, and FVC (table II). Of the 20 patients allocated to the salbutamol group, six were withdrawn at 8, 12, 16, 16, 16, and 32 hours respectively because their responses were considered to be unsatisfactory. In two cases in the aminophylline group the infusion was discontinued after 28 hours because of satisfactory clinical responses. Thus 14 patients were receiving salbutamol and 17 aminophylline 36 hours after the infusions began.

PEFR rose in both infusion groups, and rates significantly greater than those at the start of the infusion were reached after 12 hours in the aminophylline group ($P<0.02$) and 16 hours in the salbutamol group ($P<0.05$) (fig 1). As the infusion continued the mean PEFR in the aminophylline group became greater than that in the salbutamol group, although the difference was never significant. FEV_1 also rose and in both groups reached a level significantly greater than that before the infusion after 12 hours ($P<0.05$, aminophylline group; $P<0.005$, salbutamol group). The mean response was again greater in the aminophylline group (fig 2). The increase in FVC became significant 24 hours after the infusion was started in the aminophylline group

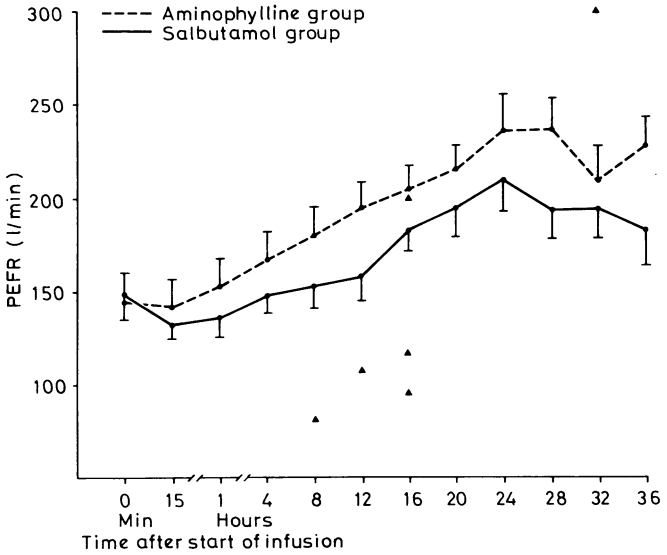

FIG 1—PEFR during infusion (mean ± SE). ▲ = PEFR in six patients at time of withdrawal from salbutamol group.

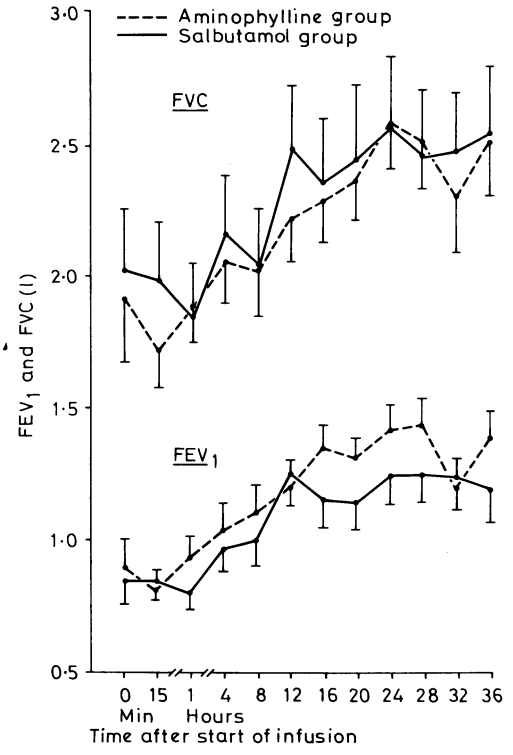

FIG 2—FEV_1 and FVC during infusion (mean ± SE).

TABLE I—*Sex and mean (± SE) age, height, and weight of patients in three treatment groups*

Group	No in group	Sex M	Sex F	Age (years)	Height in cm	Weight in kg
No infusion	23	11	12	36·7 ± 2·5	167·9 ± 1·8	63·5 ± 1·5
Aminophylline infusion	19	4	15	41·9 ± 3·3	162·6 ± 1·7	60·8 ± 2·6
Salbutamol infusion ..	20	9	11	36·2 ± 2·6	168·2 ± 1·9	63·9 ± 1·5

TABLE II—*Mean (± SE) values of pulmonary and cardiovascular function measured before and after initial treatment in the three groups*

Group	Time of observations	PEFR (l/min)	FEV_1 (l)	FVC (l)	Heart rate (beats/min)	Blood pressure (mm Hg) Systolic	Blood pressure (mm Hg) Diastolic	pH	Po_2 (kPa)	Pco_2 (kPa)
No infusion	Before	108 ± 10	0·6 ± 0·1	1·0 ± 0·1	110 ± 3	137 ± 3	83 ± 2	7·40 ± 0·01	8·0 ± 0·4	5·2 ± 0·3
	After	209 ± 16***	1·3 ± 0·1***	2·4 ± 0·2***	103 ± 4	122 ± 3**	79 ± 2			
Aminophylline infusion	Before	92 ± 9	0·6 ± 0·1	1·1 ± 0·2	107 ± 5	141 ± 6	83 ± 3	7·38 ± 0·01	7·5 ± 0·7	5·0 ± 0·1
	After	145 ± 15*	0·9 ± 0·1*	1·9 ± 0·2**	110 ± 4	127 ± 3	78 ± 3			
Salbutamol infusion ..	Before	98 ± 8	0·6 ± 0·1	1·4 ± 0·2	109 ± 4	134 ± 5	81 ± 2	7·40 ± 0·01	8·3 ± 0·3	5·1 ± 0·2
	After	146 ± 10**	0·8 ± 0·1*	2·0 ± 0·2*	115 ± 4	127 ± 4	82 ± 2			

Compared with results before treatment: * $P<0.05$. ** $P<0.01$. *** $P<0.001$.
Conversion: SI to traditional units—Po_2 and Pco_2: 1 kPa ≈ 7·5 mm Hg.

($P < 0.02$) but failed to reach levels of significance in the salbutamol group (fig 2).

There were no significant changes in heart rate and blood pressure in either group (fig 3). The mean heart rate tended to decrease in the aminophylline group but did not change in the salbutamol group. There was no fall in diastolic blood pressure in the salbutamol group.

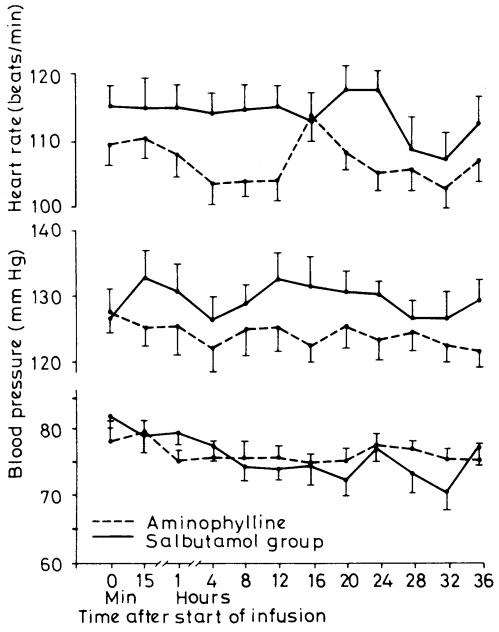

FIG 3—Systolic and diastolic blood pressures and heart rate during infusion (mean ± SE).

Discussion

This study was designed to exclude asthmatic patients whose acute attacks would respond rapidly to a short period of intensive treatment and for whom it would be unnecessary to prescribe intravenous infusion of a bronchodilator. Thus the more refractory cases were selected by their unsatisfactory response to the initial regimen.

The design of any study of acutely ill patients cannot always comply with the ideals of pharmacological trials. In this investigation the efficacy of an intravenous infusion of salbutamol in cases of severe acute asthma was not known. It was therefore considered to be unethical to perform a blind study. Similarly, it was felt that to include a placebo infusion group was unacceptable. The hospital ethical committee allowed the infusions allocated to be the only change from the accepted management programme of these patients.

Throughout the study care was taken to ensure that the physician making decisions on treatment had no part in organising the trial. Nevertheless, the possibility of physician bias against the new infusion drug was a matter of concern. The earliest time a patient allocated to salbutamol was withdrawn and given aminophylline was after eight hours. This patient and three of the remaining four withdrawn by 16 hours had PEFRs well below the mean response in the group (fig 1). The fourth patient withdrawn at 16 hours and the one withdrawn at 32 hours were subsequently found to have improved at a rate above the group mean and may have been victims of physician bias.

The overall responses of both infusion groups were similar. Any possible additional bronchodilator effect from the intravenous administration of salbutamol may have been reduced by the large regular doses of nebulised salbutamol causing saturation of the adrenoceptor sites. Nevertheless, in the only other study comparing infusions of salbutamol and aminophylline in acute asthma, in which both drugs were given for one hour as the sole treatment, both groups showed similar responses.[4]

Of the six patients in the present study who were transferred to aminophylline infusion, only one showed a subsequent increase in the rate of improvement of PEFR, FEV_1, and FVC. As aminophylline has a different mode of action from salbutamol it seems unlikely that any lack of responsiveness to salbutamol was related to the drug itself or the doses given. A more probable explanation for the slow recovery of pulmonary function in both infusion groups may be related to the natural history of recovery from acute attacks of asthma. While about one-third of all the patients recovered rapidly with the initial regimen, the rates of progress in the infusion groups were similar to the rate found in asthmatic patients receiving hydrocortisone alone.[6] Possibly, if a placebo infusion group had been included it would have yielded results similar to those of the bronchodilator infusion groups.

We could not predict from the admission data whether a patient's asthma was likely to respond to the initial regimen or would run a more chronic course. Similarly, we could not determine which patients would respond rapidly to infusion of a bronchodilator, although one-third of the patients got better rapidly without an infusion.

This study has shown that intravenous salbutamol infused at 10 μg/min may be given safely over a prolonged period to patients with acute asthma. The drug does not, however, appear to have any advantages over aminophylline when combined with the other treatments used in this study. Probably many acute attacks of asthma have a prolonged recovery course independent of bronchodilator regimens and related to mucous impaction, which may take up to 10 days to clear completely.[7]

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Requests for reprints should be addressed to SGS.

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